A Japanese Lung Cancer Registry Study

Prognosis of 13,010 Resected Lung Cancers

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Purpose: The validation of tumor, node, metastasis staging system in terms of prognosis is an indispensable part of establishing a better staging system in lung cancer.

Methods: In 2005, 387 Japanese institutions submitted information regarding the prognosis and clinicopathologic profiles of patients who underwent pulmonary resections for primary lung neoplasms in 1999 to the Japanese Joint Committee of Lung Cancer Registry. The data of 13,010 patients with only lung carcinoma histology (97.6%) were analyzed in terms of prognosis and clinicopathologic characteristics.

Results: The 5-year survival rate of the entire group was 61.4%. For the small cell histology (n = 390), the 5-year survival rates according to clinical (c) and pathologic (p) stages were as follows: 58.8% (n = 161) and 58.3% (n = 127) for IA, 58.0% (n = 77) and 60.2% (n = 79) for IB, 47.1% (n = 17) and 40.6% (n = 29) for IIA, 25.3% (n = 38) and 41.1% (n = 29) for IIB, 29.0% (n = 61) and 28.3% (n = 60) for IIIA, 36.3% (n = 19) and 34.6% (n = 40) for IIIB, and 27.8% (n = 12) and 30.8% for IV (n = 13). For the non-small cell histology (n = 12,620), the 5-year survival rates according to c-stage and p-stage were as follows: 77.3% (n = 5642) and 83.9% (n = 4772) for IA, 59.8% (n = 3081) and 66.3% (n = 2629) for IB, 54.1% (n = 205) and 61.0% (n = 361) for IIA, 43.9% (n = 1227) and 47.4% (n = 1330) for IIB, 38.3% (n = 1628) and 32.8% (n = 1862) for IIIA, 32.6% (n = 526) and 29.6% (n = 1108) for IIIB, and 26.5% (n = 198) and 23.1% (n = 375) for IV. Adenocarcinoma, female gender, and age less than 50 years were significant favorable prognostic factors.

Conclusion: This large registry study provides benchmark prognostic statistics for lung cancer. The prognostic difference between stages IB and IIA was small despite different stages. Otherwise, the present tumor, node, metastasis staging system well characterizes the stage-specific prognoses.

Key Words: Lung cancer, Surgery, Prognosis, TNM stage, Resection, Cancer registry.

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The newly revised version of the Union Internationale Contre le Cancer tumor, node, metastasis (TNM) staging system is to be promulgated for general use in 2009. The present TNM staging system for lung cancer has been available worldwide since 1978,[1] and the revision process is underway. To establish a more sophisticated, truly prognostic staging system, the validation of the existing system as well as the simulation of the proposed revision based on a large, updated data set are indispensable.

In Japan, the three major societies that deal with patients with lung neoplasms, the Japan Lung Cancer Society, the Japanese Association for Chest Surgery, and the Japanese Respiratory Society, established a task force committee (The Japanese Joint Committee of Lung Cancer Registry) to perform a nationwide registry study on the prognosis and clinicopathologic profiles of lung neoplasms, both retrospectively and prospectively. The prospective follow-up registry study has been underway for all lung cancer patients who newly visited the hospital in 2002. This prospective registry study includes both resected and nonresected cases. Beside this, the committee has periodically performed three separate retrospective studies focused on cases resected in the years 1989, 1994, and 1999 after a 5-year follow-up period. These studies were planned at 5-year intervals to observe changes and trends in the prognosis, staging, histologic distribution, etc. of resected lung cancer patients in Japan. The results of the second study for patients who were resected in 1994 have already been published elsewhere[2] together with our

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proposal for possible revisions to the present staging system.[3] The current study deals with third retrospective registry for patients who were resected in 1999.

Therefore, the purpose of the present study was to provide the most up-to-date benchmark statistics on the prognosis of resected lung cancer, and to clarify the appropriateness and insufficiencies of the present TNM staging system for lung cancer.

PATIENTS AND METHODS

Registry

In 2005, the Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study on the prognosis and clinicopathologic profiles of resected primary lung neoplasms in Japan. Only primary lung neoplasms that had been resected in 1999 at the certified teaching hospitals in Japan were considered for the registry, which had a follow-up period of at least 5 years. The Committee received the registries of 13,344 patients from 387 teaching hospitals. The questionnaire included 32 items such as gender, age, clinical (c)-T, c-N, c-M, c-stage, preoperative treatment, surgical procedure, extent of lymph node dissection, curability, residual tumor, primary site by lobe, tumor diameter, histology, organ invasion, pathologic (p)-T, p-N, p-M, p-stage, pleural involvement, pleural dissemination, intrapulmonary metastasis, pleural cytology, location of nodal metastasis, survival time, recurrence, and cause of death. Recurrent or multiple lung cancers were not included in this registry. The c-stage and p-stage were based on the 6th edition of the Union Internationale Contre le Cancer-TNM staging system published in 1997.[1] The histology of the tumor was described according to the World Health Organization classification.[4]

Patients

Sixty-nine patients (0.5%) with incomplete descriptions of their tumor histology and 265 patients with low-malignant histology or nonepithelial tumor histology (2.0%) were excluded from the study. Therefore, the present study focused on the remaining 13,010 patients with adenocarcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, or adenosquamous carcinoma. The surgical resections for these patients were various in terms of surgical mode, level of lymph node exploration, and curability. Especially, the resection was either complete in 11,528 patients (88.6%) or incomplete in 1108 patients (8.5%), and the curability was not clearly described in 374 patients (2.9%). Despite these, the TNM staging of each patient was determined on the basis of best available information before, during, and after surgical resections.

Statistical Analysis

The survival time was defined as the time from the date of surgery to the last follow-up date. The survival curves were estimated by the Kaplan-Meier method, and the difference in survival was tested by the log-rank test in which a p value of less than 0.05 was considered significant.

RESULTS

For 13,010 registered patients with lung cancer, the most common histologic type was adenocarcinoma in 8239 patients (63.3%) followed by squamous cell carcinoma in 3700 patients (28.4%), large cell carcinoma in 474 patients (3.6%), small cell carcinoma in 390 patients (3.0%), and adenosquamous carcinoma in 207 patients (1.6%). The survival curve of the entire registry population is shown in Figure 1, in which the 5-year survival rate was 61.4%. The survival curves according to histologic type of all stages are shown in Figure 2. The 5-year survival rates according to the histologic type were as follows: 67.3% for adenocarcinoma,

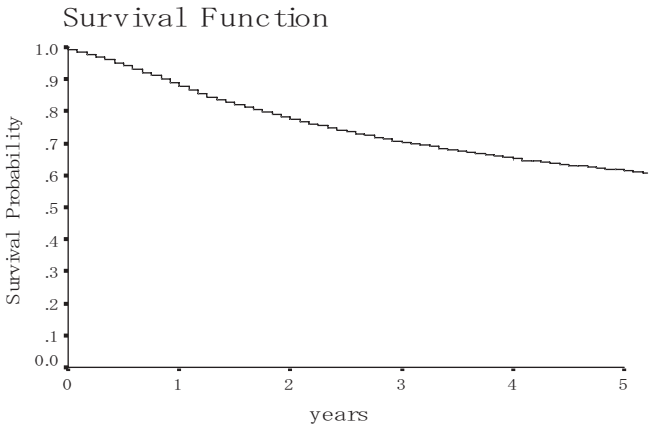

FIGURE 1. A survival curve for all histologic types and all stages (n = 13,010). The 5-year survival rate for the entire group is 61.4%.

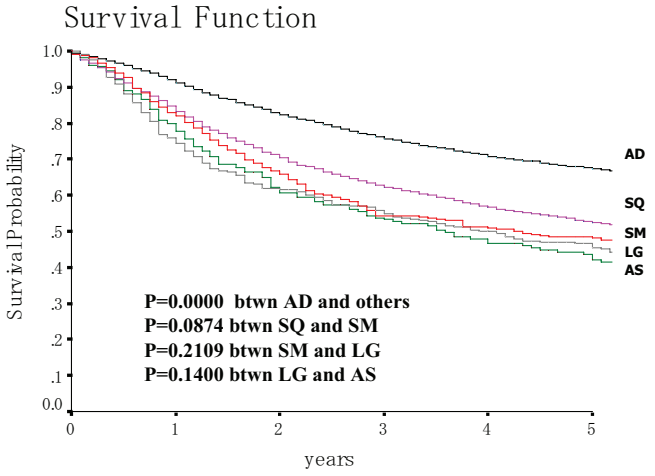

FIGURE 2. Survival curves according to histologic type. The 5-year survival rates according to histologic type are as follows: 67.3% for adenocarcinoma (n = 8239), 52.5% for squamous cell carcinoma (n = 3700), 48.1% for small cell carcinoma (n = 390), 45.5% for large cell carcinoma (n = 474), and 42.1% for adenosquamous carcinoma (n = 207). There is a significant difference in survival between adenocarcinoma and others (p = 0.0000). AD, adenocarcinoma; SQ, squamous cell carcinoma; SM, small cell carcinoma; LG, large cell carcinoma; AS, adenosquamous carcinoma.

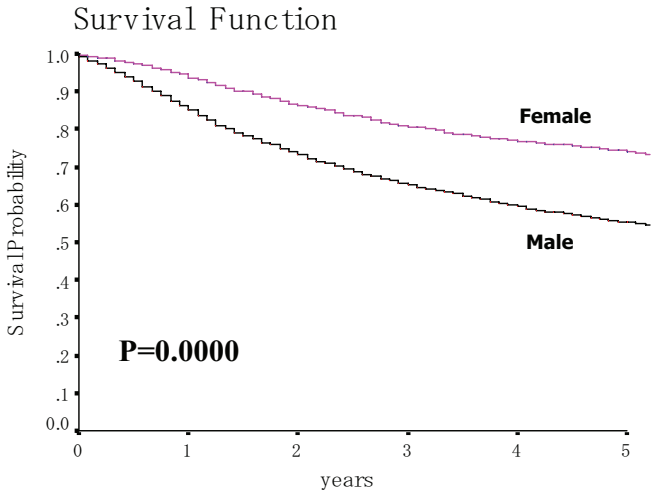

FIGURE 3. Survival curves according to gender. The 5-year survival rates of female (n = 4228) and male (n = 8664) patients are 74.1% and 55.2%, respectively. The survival of female patients is significantly better than that of male patients (p = 0.0000).

52.5% for squamous cell carcinoma, 48.1% for small cell carcinoma, 45.5% for large cell carcinoma, and 42.1% for adenosquamous carcinoma. The adenocarcinoma histology had significantly better survival than other histologic types (p = 0.0000 each). Female patients comprised 32.5% (n = 4228) of the entire registered population, and male patients comprised 66.6% (n = 8664). The 5-year survival rates of the female and male patients were 74.1% and 55.2%, respectively. These survival curves are shown in Figure 3, and the difference in survival between the 2 genders was significant (p = 0.0000). The clinical profiles and stage-specific prognosis were described separately for small cell and non-small cell histologic categories because of the known differences in the pathobiologic nature and response to treatment between these malignancies.

Small Cell Carcinoma

For 390 patients with resected small cell carcinoma of all stages, the 5-year survival rate was 48.6%. The survival curves according to stage are shown in Figure 4. The distribution of c-stage and p-stage, stage-specific 5-year survival rates, and the difference in survival between neighboring stages are presented in Table 1.

Non-small Cell Carcinoma

For 12,620 patients with resected non-small cell histologies of all stages, the 5-year survival rate was 61.8%. The survival curves according to stage are shown in Figure 5. The distribution of c-stage and p-stage, stage-specific 5-year survival rates, and difference in survival between neighboring stages are presented in Table 2. For the c-stage, the difference in survival was significant between all neighboring c-stages except for those between stages IB and IIA and between IIIA and IIIB. For the p-stage, the difference in survival was significant between all neighboring stages, although the difference between p-stages IB and IIA was approaching the marginal significance level.

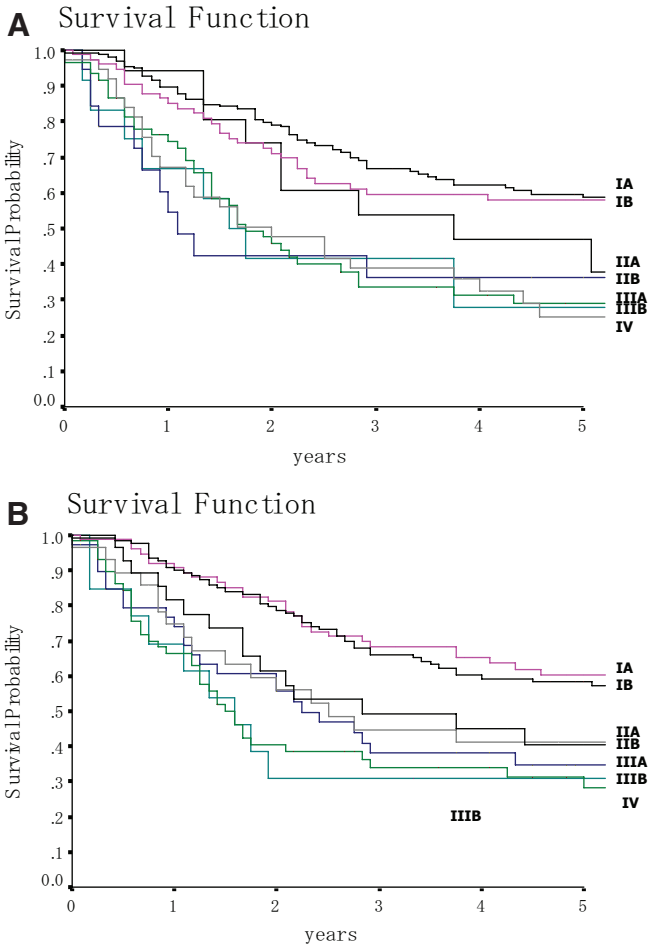

FIGURE 4. Survival curves of small cell lung carcinoma cancers according to c-stage (*A*) and p-stage (*B*) (n = 390). The 5-year survival rates by c-stage are as follows: 58.8% for IA (n = 161), 58.0% for IB (n = 77), 47.1% for IIA (n = 17), 25.3% for IIB (n = 38), 29.0% for IIIA (n = 61), 36.3% for IIIB (n = 19), and 27.8% for IV (n = 12). The 5-year survival rates by p-stage are as follows: 58.3% for IA (n = 127), 60.2% for IB (n = 79), 40.6% for IIA (n = 29), 41.1% for IIB (n = 29), 28.3% for IIIA (n = 60), 34.6% for IIIB (n = 40), and 30.8% for IV (n = 13).

Survival was further analyzed according to patient age. The survival curves according to three age groups, those $<$50 years (n = 797), those $\geq$50 years but $<$70 years (n = 6563), and those $\geq$70 years (n = 5147) are shown in Figure 6. The 5-year survival rates for the three age groups were 69.9, 66.0, and 54.9%, respectively. The survival of patients aged $\geq$70 years was significantly worse than those in the other two age groups (p = 0.0000 and p = 0.0000).

Comparison between the 1994 and 1999 Registry Studies

The distribution of histologic types was compared between 1994 and 1999 (Fig. 7). Within the 5-year interval,

TABLE 1. Stage-Specific 5-Yr Survival Rates for Small Cell Carcinoma According to the Clinical and Pathological Settings (n = 390)

	Stage						
Stage Settings	**IA**	**IB**	**IIA**	**IIB**	**IIIA**	**IIIB**	**IV**
Clinical, n (%)	161 (41.3)	77 (19.7)	17 (4.4)	38 (9.7)	61 (15.6)	19 (4.9)	12 (3.1)
5-Yr survival rate, %	58.8	58.0	47.1	25.3	29.0	36.3	27.8
Difference in survival[a]	0.5627	0.4110	0.1577	0.9807	0.7045	0.7265	—
Pathological, n (%)	127 (32.6)	79 (20.3)	29 (7.4)	29 (7.4)	60 (15.4)	40 (10.3)	13 (3.3)
5-Yr survival rate, %	58.3	60.2	40.6	41.1	28.3	34.6	30.8
Difference in survival[a]	0.9331	0.0415	0.8289	0.2300	0.5217	0.6115	—

[a] Significance of the difference in survival between neighboring (lower and next higher) stages (p value).

incidence of adenocarcinoma increased 7%, from 56 to 63%, whereas that of squamous cell carcinoma decreased 5%, from 33 to 28%. The proportion of other histologic types remained almost unchanged. When the overall survival was compared, an improvement of the 5-year survival rate from 52.0 to 61.4% was achieved for all histologic types, and from 52.6 to 61.8% for non-small cell carcinomas. The gender distribution did not change remarkably between 1994 and 1999: female patients comprised 29.9% of the all the registered patients in 1994, and 32.8% in 1999. Nevertheless, the difference in survival according to gender grew within the 5-year interval: the difference in the 5-year survival rate between women and men was 13.2% in 1994, and 18.9% in 1999.

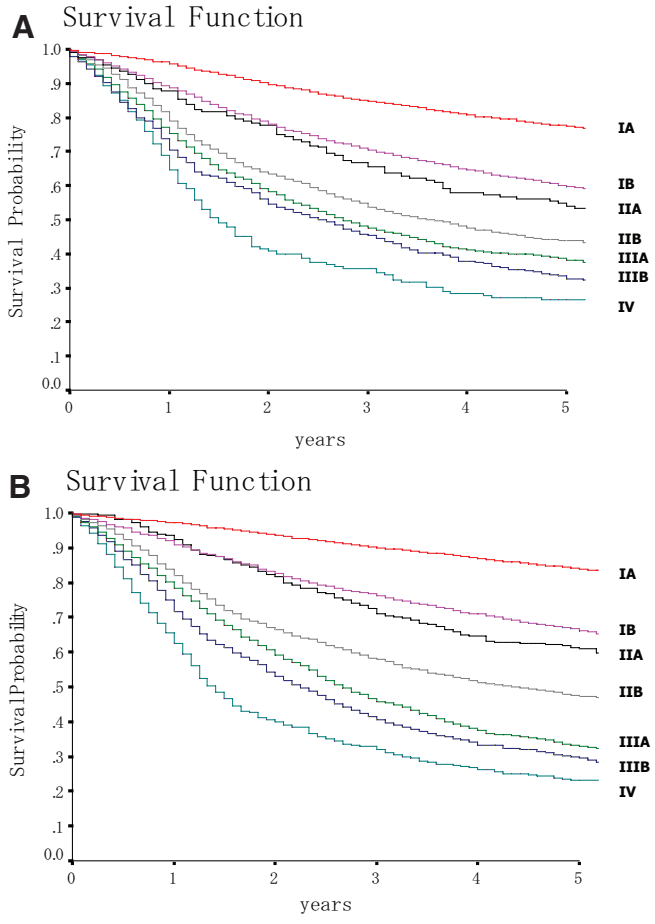

FIGURE 5. Survival curves of non-small cell histologies according to c-stage (*A*) and p-stage (*B*) (n = 12,620). The 5-year survival rates by c-stage are as follows: 77.3% for IA (n = 5642), 59.8% for IB (n = 3081), 54.1% for IIA (n = 205), 43.9% for IIB (n = 1227), 38.3% for IIIA (n = 1628), 32.6% for IIIB (n = 526), and 26.5% for IV (n = 198). The 5-year survival rates by p-stage are as follows: 83.9% for IA (n = 4772), 66.3% for IB (n = 2629), 61.0% for IIA (n = 361), 47.4% for IIB (n = 1330), 32.8% for IIIA (n = 1862), 29.6% for IIIB (n = 1108), and 23.1% for IV (n = 375).

The stage distribution was compared in non-small cell lung carcinoma between 1994 and 1999 (Fig. 8). The percentage of stages IA and IB increased 11%, from 59 to 70%, in the c-setting, and 8%, from 51 to 59%, in the p-setting. Stage-specific 5-year survival rates in non-small cell carcinoma were compared between the 1994 and 1999 registry studies for c-stage (Table 3) and for p-stage (Table 4). Although a survival improvement was achieved in all stages, the change in stage IB was remarkable. The 5-year survival rate in stage IB improved from 49.9 to 59.8% in a c-setting, and from 60.1 to 66.3% in a p-setting. Summarizing these, the trends from 1994 to 1999 consisted of an increase in the adenocarcinoma histology and earlier stages, and an improvement in the overall as well as the stage-specific survival.

DISCUSSION

This is a report on the third nationwide registry study conducted by the Japanese Joint Committee of Lung Cancer Registry representing three major Japanese societies that deal with patients with lung cancer, in which the clinicopathologic features and prognosis of the resected lung cancer were studied. Three registry studies have independently and periodically focused on cases that were resected in the years 1989, 1994, and 1999 after a 5-year follow-up period. The details of the second study involving cases resected in 1994 in which 7393 patients with primary lung neoplasms were registered from 307 teaching hospitals in Japan have already been published elsewhere.[2,3] The number of registered patients in the third study (13,344 patients) was almost twice that of the second study (7393 patients) with only a slight increase in the number of participating institutions from 307 to 387. The number of cases registered from each institute ranged from 1 to 212 cases, and 15 institutes registered more than 100 cases. Considering that the total number of lung

TABLE 2. Stage-Specific 5-Yr Survival Rates for Non-small Cell Carcinoma According to the Clinical and Pathological Settings (n = 12,620)

	Stage						
Stage Settings	**IA**	**IB**	**IIA**	**IIB**	**IIIA**	**IIIB**	**IV**
Clinical, n (%)	5642 (44.7%)	3081 (24.4%)	205 (1.6%)	1227 (9.7%)	1628 (12.9%)	526 (4.2%)	198 (1.6%)
5-Yr survival rate, %	77.3	59.8	54.1	43.9	38.3	32.6	26.5
Difference in survival[a]	0.0000	0.1444	0.0022	0.0013	0.0755	0.0111	—
Pathological, n (%)	4772 (37.8%)	2629 (20.8%)	361 (2.9%)	1330 (10.5%)	1862 (14.8%)	1108 (8.8%)	375 (3.0%)
5-Yr survival rate, %	83.9	66.3	61.0	47.4	32.8	29.6	23.1
Difference in survival[a]	0.0000	0.0367	0.0000	0.0000	0.0054	0.0001	—

[a] Significance of the difference in survival between neighboring (lower and next higher) stages (p value).

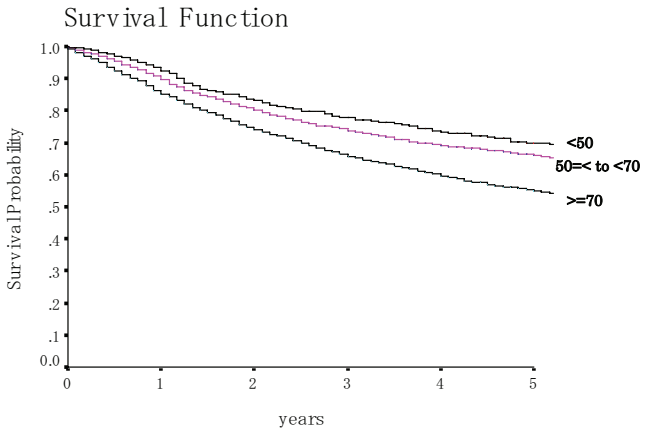

FIGURE 6. Survival curves according age in non-small lung cancer. The 5-year survival rates for the three age groups, <50 years (n = 797), ≥50 years but <70 years (n = 6563), and ≥70 years (n = 5147) are 69.9%, 66.0%, and 54.9%, respectively.

cancer resections in Japan was approximately 30,000, these registered cases are estimated to comprise 30 to 40% of the total. The results of this registry study represent the findings based on the largest series ever published.

There has been remarkable difference in survival between patients resected in 1994 and 1999, where the overall survival rate at 5 years in the registry population improved from 52.6 to 61.4%. The stage-specific survival also improved. Because the survival improvement was achieved not only in all stages but also in the entire population, this improvement should not be interpreted as simply the result of a stage migration phenomenon. The possible reasons for the improvement might be refinements in the evaluation of surgical candidates, advancements and improvement in treatment, and the shift of the registry population toward more curable lung cancer.

Refinement in the preoperative work-up for surgical candidates may better identify patients with distant disease, resulting in a better selection of patients for surgery. Nevertheless, except for an improvement in imaging diagnosis techniques such as computed tomography (CT), the difference in the quality of preoperative work-up between 1994 and 1999 does not seem significant. Even in 1999, positron emission tomography scans were not used as part of a routine preoperative work-up in Japan. Therefore, the difference in preoperative work-up does not seem to account for the difference in survival between the years 1994 and 1999.

When looking at the changes in surgical interventions for lung cancer patients in the 5 years between 1994 and

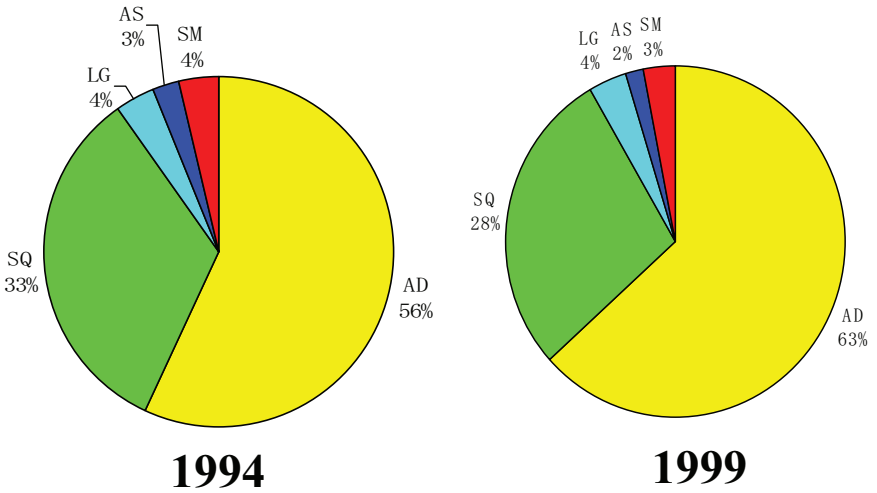

FIGURE 7. Distribution of histologic types in 1994 and 1999. Adenocarcinoma increases 7% (from 56% to 63%) and squamous cell carcinoma decreases 5% (from 33% to 28%).

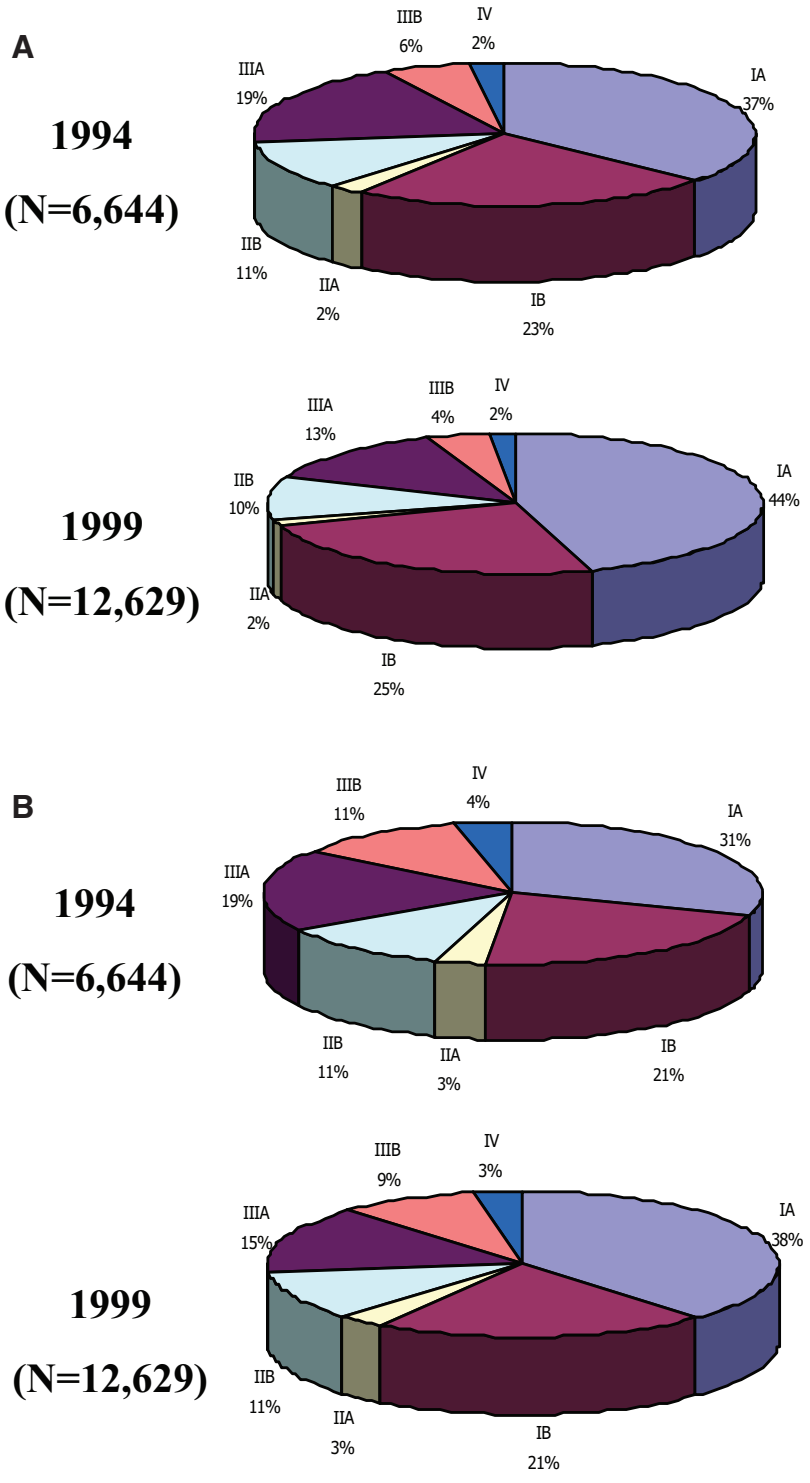

FIGURE 8. Distribution of c-stage (*A*) and p-stage (*B*) for non-small cell lung histologies in 1994 and 1999. The percentage of stage I increased from 60 to 69% (11%) in the c-setting, and from 52 to 59% (7%) in the p-setting.

1999, we recognized that less (or minimally) invasive surgery with or without video assistance had been more generalized.[5] In these minimally invasive techniques, the faster postoperative recovery has been speculated, and this is a present-day trend in oncologic surgery of any sites. Nevertheless, knowing that no one study has ever definitely demonstrated that minimally invasive surgery improves the survival of patients with lung cancer, or the mortality/morbidity, it is unlikely that the improvement in survival of the present registry population was solely because of the advancements in surgical interventions.

Comparing the distribution of histologic types between 1994 and 1999, the 7% increase in adenocarcinomas and the 5% decrease in squamous cell carcinoma were remarkable changes. In this registry study, the noninvasive form of

TABLE 3. Comparison of Stage-Specific 5-Yr Survival Rate (%) between 1994 and 1999 (c-Stage) in Non-small Cell Histologies

	c-Stage							
Year of Survey	**IA**	**IB**	**IIA**	**IIB**	**IIIA**	**IIIB**	**IV**	**All Stages**
1994 (n = 6,644)	72.1	49.9	48.7	40.6	35.8	28.0	20.8	52.6
1999 (n = 12,620)	77.3	59.8	54.1	43.9	38.3	32.6	26.5	61.8

TABLE 4. Comparison of Stage-Specific 5-Yr Survival Rate (%) between 1994 and 1999 (p-Stage) in Non-small Cell Histologies

	p-Stage							
Year of Survey	**IA**	**IB**	**IIA**	**IIB**	**IIIA**	**IIIB**	**IV**	**All Stages**
1994 (n = 6,644)	79.5	60.1	59.9	42.2	29.8	19.3	20.0	52.6
1999 (n = 12,620)	83.9	66.3	61.0	47.4	32.8	29.6	23.1	61.8

adenocarcinoma, nonmucinous bronchioloalveolar carcinoma, was included in the adenocarcinoma category. These tumors are well known for their characteristic presentation on high-resolution CT images as ground glass opacity and a superb prognosis without recurrence after intervention.[6,7] Considering that the evaluation of these faint, small-sized tumors using high-resolution CT was being generalized in Japan in late 1990s, the increase in bronchioloalveolar carcinoma might have resulted in the inclusion of these earlier, less-aggressive tumors into the registry population. The distribution of the stage of the disease at diagnosis also changed remarkably between 1994 and 1999 as can be seen in Figure 8. The earliest disease, stage IA and IB, comprised 60% of the c-stage and 52% of the p-stage in 1994, and 69% and 59% in 1999, respectively. The shift of the patients' diagnosis toward an earlier staged disease at the time of surgery definitely had a significant impact on the improvement in overall survival.

Based on the second registry study of cases resected in 1994, we proposed a revision of the TNM staging system in which the unification of stages IB and IIA and the division of T1 into T1a and T1b by the cutoff length of a diameter of 2 cm were shown to be necessary. In this latest 1999 data set the prognostic difference in survival between stages IB and IIA was small. In the c-setting, the 5-year survival rates for IB and IIA were 59.8% and 54.1%, and the difference in survival was not statistically significant ($p = 0.1444$). In the p-setting, the 5-year survival rates for IB and IIA were 66.3% and 61.0%, and the difference in survival was marginally significant ($p = 0.0367$), probably because of the increase in the overall number of patients. Because the survival improvement in patients with stage IB was so remarkable, the prognostic difference between stages IB and IIA seemed to increase in 1999 compared with that in 1994. Nevertheless, considering the limited number of patients with stage IIA disease, we believe that the unification of stages IB and IIA would well characterize the stage-specific prognosis of both groups.

In the report on the second registry study, the large prognostic difference in survival by gender, age, and histology was addressed. Also, in this third registry study, a significant difference in survival according to these variables was reproduced. Especially, the difference in 5-year survival rate by gender was almost 20% in non-small cell carcinomas, in which the 5-year survival rates for men and women were 55.5% and 74.5%, respectively. It is still unclear what factors account for the large survival difference between men and women. It is necessary to see the relationship between female gender and other significant prognostic variables such as histology and their biologic characteristics. Considering the difference in smoking status between the two genders in Japan, the difference in the biologic nature of cancers in women versus men might have some impact on overall survival.

The present retrospective, nationwide, large-scale registry study provides the most updated benchmark statistics for patients with lung cancer. Further studies to elucidate the factors associated with the improvement of survival and the impact of several prognostic variables is underway.

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